Exposure to Cigarette Smoke and Cervical Cancer

To the Editor.—We would like to comment on the article by Slattery et al[1] entitled "Cigarette Smoking and Exposure to Passive Smoke Are Risk Factors for Cervical Cancer."

In case-control studies there is always the danger of overmatching or undermatching in selection of control subjects. In this report, there clearly is undermatching of control patients with regard to important risk factors including sexual activity, religious background, and education. For example, 52% of control subjects vs only 10% of case subjects reported having fewer than two sexual partners; 75% of control subjects but only 49% of case subjects were high school graduates; and 58% of control subjects vs 18% of case subjects were frequent churchgoers. Since the previously mentioned risk factors are correlated highly with one another as well as with active and passive smoking, the risk estimates relating smoking and cervical cancer may be subject to substantial bias and confounding. This has been demonstrated in logistic regression analyses when the variables show high multicolinearity.[2] It is fallacious to expect multivariate techniques such as logistic regression to correct all the resultant confounding and biases. The effect of adjustment on odds ratios is far greater than expected in case-control studies of this sort, as, for example, the decrease from 14.84 to 2.96 for passive smoke exposure. In fact, the adjusted odds ratios are probably no more than the leftover effect of variables controlled imperfectly by logistic regression.

Another potential source of confounding for which there is a complete lack of information concerns the smoking behavior and sexual activities of male sexual partners. The apparent association between cervical cancer and environmental smoke exposure may, in fact, be the result of increased exposure to papillomaviruses or herpes simplex virus 2 through contact with male sexual partners who smoke, since one might expect smokers to be generally more sexually active than nonsmokers, and case patients are more sexually active than control subjects.

In addition, when case and control subjects are compared with regard to the number of sexual partners, the actual difference could be underestimated easily because of the expected tendency among case subjects to underreport their higher level of sexual activities.

Furthermore, no information is given about the age at which sexual activities began, although early promiscuity is a known risk factor for cervical cancer and probably is related to smoking as well. This important issue of sexual behavior vis-à-vis smoking and cervical cancer is confounded further by the fact that monogamous and celibate participants were combined into a single category in the analyses, although their exposure to both environmental smoke and sexually transmitted infections clearly is not equal.

Finally, a comment on biologic plausibility. As stated in the article, colleagues at our institute have reported the presence of cotinine in cervical mucosa.[3] However, the mean concentration of cotinine in passive smokers is less than 1% of that observed in active smokers. Furthermore, no nitrosamines or other carcinogens thus far have been isolated successfully from cervical mucosa, even in heavy smokers. It is highly unlikely that the carcinogenic effect of passive and active tobacco smoke exposures is approximately equal (with odds ratios of 2.96 and 3.42, respectively), as reported by the authors.

In view of the previously mentioned considerations, the classification of passive smoke exposure as a risk factor for cervical cancer seems premature.

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2. McGee D, Reed D, Katsuhiko Y. The results of logistic analyses when the variables are highly correlated. *J Chronic Dis*. 1964;37:713-719.
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In Reply. — Control patients were matched to case patients by age in our study, while sexual history, education, and church attendance (to help control for sexual activity) were controlled in the smoking analyses so that they also could be examined as independent risk factors in other analyses.[1] Because of the risk of cervical cancer associated with these variables,[2] major differences in their distribution between case and control subjects were noted. These variables, although associated, did not present, in the analysis, a problem of multicolinearity. While logistic regression models have the capability to control for confounding, they can only control to the extent that the data are accurate. Thus, biased risk estimates could result if important confounding variables were reported inaccurately, although they were controlled in the analyses. While there is the possibility that sexual history is reported inaccurately, we do not believe that case patients reported differently than control patients because they were unaware that we were studying cervical cancer. The reported number of sex partners of the woman was used to control for sexual activity patterns; results were qualitatively the same when adjusting for the number of sexual partners of the man; age at first intercourse was not related to cervical cancer after controlling for the number of sexual partners.[1] It is possible that either human papillomavirus or type-specific herpes simplex virus 2 may be partially confounding the observed association; at present, we are unable to explore this issue in more detail.

At this point, we can only speculate how active or passive smoking can biologically be related to cervical cancer. The risk estimates observed for cigarette smoking are similar to those reported elsewhere in the literature, which gives credence to our findings. The risk estimates associated with passive smoking should not be inflated or more biased than those associated with actual smoking because of inadequate recall or uncontrolled confounding. Based on our results, we believe that this association should be verified in other studies. Lastly, as pointed out by Dr Layde in his editorial,[2] while we do not know of a biologic mechanism for either active or passive smoking to be related to cervical cancer, we do know that cigarette smoking is harmful to health. The message to the public, as a result of this study, is one that reinforces the message that smoking is detrimental to health.

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1. Slattery ML, Overall JC Jr, Abbott TM, et al. Sexual activity, contraception, genital infections and cervical cancer: support for a sexually transmitted disease hypothesis. *Am J Epidemiol*. In press.
2. Layde PM. Smoking and cervical cancer: cause or coincidence? *JAMA*. 1989;261:1631-1633.

Amateur Boxing

To the Editor.—I was disappointed and dismayed by the misleading article on boxing in the January 6 issue of *JAMA*.[1] Juan Antonio Samarach, president of the International Olympic Committee, publicly stated his support for including boxing in the Olympic program. The committee's investigation of boxing was directed toward reviewing the scoring system.

It is unfair to lump all types of boxing together. Professional and amateur boxing have vastly different rules, objectives, and requirements. No matter what television commentators might say, the style and technique are not the same. To combine events and actions of the two types of boxing in one article totally misrepresents the facts. Moreover, the boxing programs for police